

## PATENT SPECIFICATION

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## (54) COMPOSITIONS IN THE FORM OF COATED TABLETS

(71) We, NIPPON KAYAKU KABUSHIKI KAISHA, of No. 2-1, Marunouchi 1-chome, Chiyoda-ku, Tokyo, Japan, and HAYASHIBARA BIOCHEMICAL LABORATORIES INC., of 2-3, Shimoishii 1-chome, Okayama-shi, Japan, both Japanese companies, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to compositions in the form of tablets prepared by a direct compression method.

There are three general methods of preparing tablets. One method is the wet granulation method wherein a pharmacologically active ingredient is mixed with an excipient (i.e. a carrier) and the mixture is blended with water or an organic solvent and is then kneaded, granulated, dried, sieved and then a lubricant is mixed with the granules and the mixture is compressed to form tablets. A second method is the dry granulation method wherein a pharmacologically active ingredient is mixed with an excipient and the mixture is granulated in a dry granulator and then the granules are compressed to form tablets. With this method, however, the compression characteristics of the tablets are usually inferior because of the variation of the properties of the granules produced by this method. A third method is the direct compression method wherein a pharmacologically active ingredient is mixed with an excipient and then the mixture is compressed to form a tablet without the granulating step.

Recently, the direct compression method has become important, and has replaced the other methods because the direct compression method does not require a kneading step, a granulating step, a drying step and a sieving step as in the wet granulation method, and accordingly it is advantageous in time and cost and also from the point of view of the stability of the pharmacologically active ingredient i.e. the active ingredient is in some cases adversely affected by the steps carried out in the wet

granulation method. However, the advantages of the wet granulation method are that the fluidity of powders originally having low fluidity is increased by the granulation step and a suitable granule strength can be achieved so that the tablets can easily be prepared. On the other hand, in the direct compression method, it is known that there are few excipients which have satisfactory compression characteristics and have satisfactory compatibility and stability (both against loss of potency of the active ingredient e.g. an enzyme caused by high pressure during compression [(Yakuzaigaku 33 (1) 1—5, 1973, and 33 (1) 5—9, 1973; Pressure inactivation of digestive enzymes (II) (III). Tsuneo Uchida et al (Chugai Pharmaceutical Co. Ltd. Ukima Factory)] and against physical disintegration of the tablet over a period of time).

Heretofore, microcrystalline cellulose has been used as the optimum excipient for the direct compression method. However, a tablet containing microcrystalline cellulose as an excipient and prepared by the direct compression method has a high expansion coefficient in a highly humid atmosphere. Accordingly, sugar coated tablets containing microcrystalline cellulose have the disadvantage that the coating tends to crack. Moreover, the disintegration of a tablet containing microcrystalline cellulose has a high dependency on the compressive force used to form the tablet and is quite low when the tablet is compressed at more than a certain limit whereby the dissolution of the active ingredient is too low to impart effectiveness.

According to one aspect of the invention there is provided a composition in the form of coated tablets prepared by the direct compression method as herein defined which comprises a pharmacologically active ingredient and maltose.

In another aspect the invention provides a method for making such a preparation which includes the steps of mixing a pharmacologically active ingredient with maltose, directly compressing the mixture into tablets and coating the tablets.

It is an advantage of the invention at least in preferred forms, that it is can provide a tablet composition prepared by a direct compression method which has good compression characteristics and high hardness, these characteristics being substantially the same as those of tablets prepared by using microcrystalline cellulose, and which also has an expansion coefficient in a humid atmosphere which is remarkably lower than that of a tablet prepared by using microcrystalline cellulose. The tablets also have substantially no decrease of activity during the compressing step and a desirable rate disintegration and a sweet taste.

The maltose composition used in the invention is usually prepared by severing the  $\alpha$ -1,6-glucoside bond of a starch by means of  $\alpha$ -1,6-glucosidase in order to convert the starch to straight chain compounds and then treating the resulting product  $\beta$ -amylase which can be used for foods or pharmaceutical compositions.

When a tablet is prepared by using maltose as the excipient by the direct compression method, it is possible to mix with the composition a lubricant, another adjuvant and a disintegrant as used in conventional pharmaceutical compositions. Any pharmacologically active ingredient may be used to form the composition of the invention provided it is suitable for forming tablets. The content of the pharmacologically active ingredient is usually in the range of 0.1—85 wt.%, and the content of maltose is usually in the range of 5—99.8 wt.% and preferably 10—99 wt.%. When the fluidity and compression characteristics of the pharmacologically active ingredient are high, the content of maltose can be low and when the fluidity and compression characteristics of the active ingredient are low, the content of maltose is preferably high. In general, it is preferable to use a high content of maltose in order to produce a sweet taste.

It is also usual for the compositions to contain other adjuvants, a disintegrant and a lubricant in addition to the active ingredient and maltose. Other adjuvants which can be used in the composition, include crystalline lactose, mannitol, sorbitol, calcium sulfate and anhydrous calcium phosphate. The content of the other adjuvants is preferably in the range of 0—30 wt.%. Typical disintegrants which may be used include cornstarch, potato-starch, calcium carboxymethyl cellulose and hydroxypropyl-starch. The content of the disintegrant is usually in the range of 0—20 wt.%. Typical lubricants include talc, silicon dioxide powder, magnesium stearate, stearic acid and palmitic acid. The content of the lubricant is preferably in the range of 0.1—2.0 wt. %.

The resulting mixture is directly compressed in a tableting machine for example a single

punch tableting machine or a rotary tableting machine.

The coating on the tablets is preferably of sugar.

The advantages of tablets prepared according to the invention will be illustrated by the following Experiments.

#### EXPERIMENT 1.

##### Maximum hardness test and disintegration test.

##### (1) Test Method:

99.5 wt. parts of maltose was mixed with 0.5 wt. part of magnesium stearate. A tableting machine equipped with a pestle (a tableting punch) having a diameter of 10 mm and a curvature of 7.5 R, and a strain gauge operated by the pestle was used to form tablets having a weight of 270 mg and a hardness of 6 kg at a thickness of 5.00 mm from the mixture, the mixture being compressed at varying pressures. The average pressure of the upper pestle and the lower pestle was recorded and the hardness of the resulting tablets was measured by an Erweka hardness tester in order to discover the maximum hardness (tablet A of the invention). (the hardness of the tablets increases as the pressure increases until a maximum is achieved after which the hardness is no longer increased and is often reduced). A disintegration test on the tablets was conducted according to Pharmacopoeia of Japan Vol 8 Pages 824—846 "Disintegration test method".

As a reference, the process described above for preparing tablets was repeated except that a microcrystalline cellulose was used instead of the maltose and the weight of the tablet was varied to 235 mg (tablet B as a control).

As a further reference, 97.5 wt. parts of a mixture of lactose and cornstarch (in a weight ratio of 3:1) was mixed with 2 wt. parts of polyvinylpyrrolidone and granules of the mixture were formed by a wet granulation method. The granules were mixed with 0.5 wt. parts of magnesium stearate. The process for preparing a tablet was repeated except for using the stated mixture and varying the weight of the tablet to 290 mg (tablet C is a control).

##### (2) Test Results.

(a) Relations of pressure to hardness (maximum hardness test).

The test results are shown in Figure 1 wherein the curve A shows the relation of the hardness of tablets prepared by using maltose according to the invention (ordinate) to the compressing pressure (abscissa); the curve B shows that of the tablets prepared by using microcrystalline cellulose; and the curve C shows that of the tablets prepared by using lactose and cornstarch. It is clear from the results of Figure 1 that the tablet prepared by using maltose has substantially the same compression characteristics as the tablet prepared by using microcrystalline cellulose. On

the other hand, the maximum hardness of the tablet prepared by using lactose and cornstarch was low causing "capping" at a hardness of about 12.5 kg.

- 5 (b) Relation of pressure to disintegration (Disintegration test): The test results are shown in Figure 2, wherein the curve (A') shows the relation of the time for the disintegration of a tablet prepared by using maltose according to the invention (ordinate) to the compressing pressure (abscissa); the curve (B') shows that of the tablet prepared by using microcrystalline cellulose and the curve (C') shows that of the tablet prepared by using lactose and cornstarch.

- 10 It is clear from Figure 2 that the tablet prepared by using maltose at a typical pressure of 1000—2000 kg is disintegrated in a short time period without the pressure dependency of the time for disintegration. This is quite superior to that of the tablet prepared by using microcrystalline cellulose. The tablets prepared by using lactose and cornstarch have relatively low pressure dependency of the time for disintegration, but has the above-mentioned disadvantage of low maximum hardness. The tablet prepared by using maltose thus has excellent advantages on both of tests (a) and (b).

- 15 30 **EXPERIMENT 2.**  
Friability test and weight and thickness

increasing test in various relative humidity:

(1) *Preparation of Sample.*

99.5 wt. parts of maltose was mixed with 0.5 wt. part of magnesium stearate. A tabletting machine equipped with a pestle having a diameter of 10 mm and a curvature of 7.5 R (7.5 mm), was used to compress directly tablets having a hardness of 5 kg (tablet according to the invention) from the mixture. As a reference, the process was repeated except that microcrystalline cellulose was used instead of maltose (reference tablets).

(2) *Test Method.*

(i) Friability tests on the tablets were conducted using a Roche type friabilator.

(ii) The weight and thickness increasing test in various relative humidity were conducted at 25°C.

(3) *Test Result.*

The test results are shown in Tables 1 and 2.

Table 1 (Rate of friabilated residue in weight percentage by the Roche friabilator).

	Invention	Reference
Test period 10 minutes	99.95%	99.90%

TABLE 2

(Weight and thickness increase of tablets in various relative humidities at 25°C after 2 days)

		Tablet at preparation time	52% RH	74% RH	84% RH
Invention	weight	280 mg	+0.43%	+2.21%	+2.16%
	thickness	5.07 mm	+0.01 mm	+0.035 mm	+0.036 mm
Control	weight	240 mg	+0.30%	+2.38%	+2.29%
	thickness	5.17 mm	+0.006 mm	+0.118 mm	+0.110 mm

- 65 It is clear from the results of Table 1 of the friability test that there is substantially no difference between the tablet of the invention and that of the reference (control). However, in the results of Table 2, the rate of weight increase of the tablet of the invention was substantially the same as that of the control nevertheless, the rate of thickness increase of the control tablet was about 3 times that of the invention at higher than 74% relative humidity. This fact shows the remarkable advantages of the tablets of the invention. It is clear that the high expansion coefficient of microcrystalline cellulose causes cracking of sugar coated tablet.

In the following examples, 'n' is used to indicated the number of tablets used in each test.

Example 1.

50 g. of 2,4'-dimethyl-3-piperidinopropiophenone was mixed with 1 g of silicic anhydride powder and then 150 g of maltose and 42 g of cornstarch were added and mixed following which 2 g of magnesium stearate was added and mixed. A tabletting machine equipped with a pestle having a diameter of 9.0 mm and a curvature of 7.0 R was used to form continuously tablets from the resulting mixture having a weight of 245 mg and a thickness of 2.65 mm at a rate of 70 tablets

per minute. As a result, excellent tablets having a coefficient of variance of weight ( $n=50$ ) of 1.3%, a hardness ( $n=20$ ) of  $5.5 \text{ kg} \pm 1 \text{ kg}$  and a time for disintegration ( $n=6$ ) of 2—3 minutes and a rate of friabilated residue of 99.95% were obtained. The maximum hardness of the mixture was higher than 15 kg. Sugar coated tablets were prepared using the resulting tablets in the conventional way.

The sugar coated tablets were kept in an atmosphere of 74% relative humidity at  $50^\circ\text{C}$  to observe the cracking condition of the tablets.

50 g. of 2,4' - dimethyl - 3 - piperidino-propionophenone was mixed with 1 g of fine silicon dioxide powder and then 50 g of microcrystalline cellulose and 117 g of crystalline lactose were mixed therewith, and then 2 g of magnesium stearate was further mixed. The same tableting machine equipped with a pestle having a diameter of 9.0 mm and a curvature of 7.0 R was used to form continuously tablets from the resulting mixture having a weight of 220 mg, a thickness of 2.65 mm and a hardness of  $5.5 \text{ kg} \pm 1 \text{ kg}$ . Sugar coated tablets were prepared using the resulting tablets in the conventional way. The cracking condition of the sugar coated tablets was also observed as reference.

It was found that 100% of the sugar coated tablets prepared by using microcrystalline cellulose were cracked within 3 days from the initiation. On the other hand, only 30% of the sugar coated tablets prepared by using maltose were cracked within 14 days from the initiation.

#### Example 2.

A mixture of 15 g of bromelain (10,000 bromelain units = about 15 mg) and 30 g of cornstarch was mixed with 98.5 g of maltose, and then 1.5 g of magnesium stearate was further mixed therewith. A single punch tableting machine equipped with a pestle having a diameter of 7.5 mm and a curvature of 5.5 R was used to form continuously tablets from the resulting mixture having a weight of 145 m, a thickness of 3.7 mm, a hardness of 4—5 kg and a time for disintegration of 2—3 minutes at a rate of 70 tablets per minutes. The potency of bromelain as a powder was 10,300 units and the potency of bromelain in tablet form was 10,300 units. Thus, no variation of potency was found.

On the other hand, tablets were prepared by a conventional granulating method using lactose instead of the maltose. The potency

of bromelain as the granules was 9800 units per 145 mg, but the potency of bromelain as the tablet was 9,250 units which is about 6% lower than that of the granules. The tablets were coated with a coating solution containing 10 wt. parts of celluloseacetate, phthalate, 3 wt. parts of purified sesame oil, 30 wt. parts of acetone and 53 wt. parts of 2-ethoxyethanol, to obtain intestinal soluble tablets of bromelain.

#### WHAT WE CLAIM IS:—

1. A pharmaceutical preparation in the form of coated tablets prepared by the direct compression method as herein defined which comprises a pharmacologically active ingredient and maltose.

2. A preparation according to claim 1 which comprises 5—99.8 wt. % of maltose and 0.1—85 wt. % of the pharmacologically active ingredient.

3. A preparation according to claim 1 or claim 2 which further comprises 0.1—2 wt. % of a lubricant; 0—30 wt. % of an adjuvant; and 0—20 wt. % of a disintegrant.

4. A preparation according to claim 3, wherein the lubricant is talc, silicon dioxide powder, magnesium stearate, stearic acid or palmitic acid.

5. A preparation according to claim 3 or claim 4 wherein the adjuvant is selected from crystalline lactose, mannitol, sorbitol, calcium sulfate or anhydrous calcium phosphate.

6. A preparation according to any one of claims 3 to 5 where the disintegrant is cornstarch, potato-starch, calcium carboxymethyl cellulose or hydroxypropylstarch.

7. A preparation according to any preceding claim wherein the tablets are sugar coated.

8. A preparation according to claim 1 substantially as described herein with reference to the Examples.

9. A process for making a preparation according to any one of the preceding claims which includes the steps of mixing a pharmacologically active ingredient with maltose, directly compressing the mixture into tablets and coating the tablets.

10. A process according to claim 9 substantially as herein described with reference to the Examples.

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FIG. 1

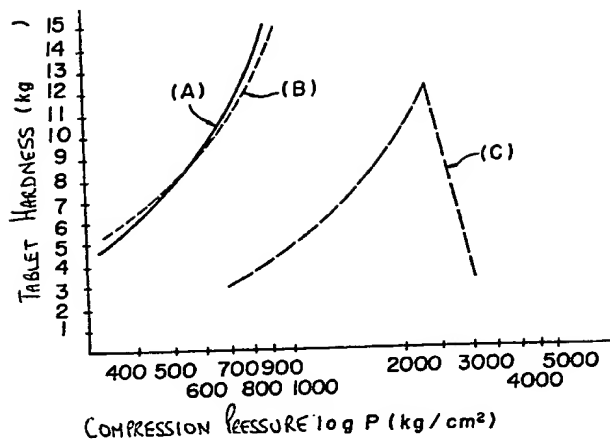


FIG. 2

